STUDIES ON THE BASOPHILIC GRANULATIONS OF THE ERYTHROCYTE IN LEAD POISONING AND OTHER CONDITIONS, WITH SPECIAL REFERENCE TO THE RELATION WHICH THEY BEAR TO THE NUCLEI OF THE RED BLOOD CORPUSCLES.

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The etiology and significance of basophilic granulations occurring in the erythrocytes of the circulating blood of man have been much discussed in recent years and variously interpreted. These granulations were seen by many of the earlier writers in the erythrocytes of individuals presenting various forms of anæmia. By some, they were thought to represent the remains of a pre-existing nucleus, and their presence seemed to indicate the means whereby the normoblast lost its nucleus and became an adult red corpuscle.

Grawitz[1] found basophilic granules in cases of pernicious anæmia, not only in the erythrocytes, but also in the nucleated red blood corpuscles. The erythrocytes containing these granules he noticed increased in numbers as the anæmia became more severe, and decreased with improvement. They were, however, entirely absent in the bone-marrow of severe cases. He also found them present in the blood of more than thirty cases of lead poisoning, their numbers being in direct proportion to the severity of the symptoms, while in some cases they were the only sign of lead poisoning. The fact that granules were frequently found in the protoplasm of nucleated cells, the nucleus of which was apparently normal, he thought was evidence that the granules were not the product of nuclear fragmentation.

As a result of his studies Grawitz concluded that these granules are due to a degenerative process affecting the hæmoglobin of the red corpuscles, a condition which is produced by the action of some definite blood poison.

White, Pepper,[2] and Stengel[3] examined the blood of twenty-one lead workers without subjective symptoms, and found basophilic granules in the red corpuscles of every case. In five of their cases they found small numbers of nucleated red corpuscles in each slide, but they do not speak of having made a total count of the erythrocytes. They were able to demonstrate the granules in red corpuscles of dogs after administering small doses of lead acetate by mouth, and found that in all their experimental cases the earlier granules showed a greater tendency to clump and cling together than did the later. They also state that in their experiments upon dogs it was a very common observation to find nucleated red corpuscles associated with the granular cells.

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[1] American Journal of the Medical Sciences, 1900, vol. cxx. p. 278

[2] Ibid., 1901, vol. cxxii. p. 266.

[3] Ibid., 1902, vol. cxxiii. p. 873.

Simon[1] studied the blood of twenty cases of lead poisoning and found basophilic granules constantly present in the red blood corpuscles. He was also able to demonstrate granules in the red blood cells of two of his fellow-workers seventy-two hours after the administration of six grains of lead acetate by mouth. In one of these experiments the lead acetate was continued until abdominal pain and constipation were produced. The lead was then stopped and many granular cells were found in the blood. Six days after this one normoblast was found in one slide studied, but this individual he states was somewhat anæmic, as indicated by a slight reduction of the hæmoglobin percentage. He makes no mention of a total count of the red blood corpuscles per 1 c.mm. White, Pepper, Stengel, and Simon all seem to agree with Grawitz as to the origin and significance of these granulations.

Schmidt[2] performed a series of interesting experiments upon animals poisoned by lead salts and phenol-hydrazine, by which means he was able to demonstrate the presence of many granular cells as well as nucleated red corpuscles in the peripheral circulation. He states that there was no essential difference between lead poisoning and phenol-hydrazine poisoning in his experimental cases. Further, he injected a rabbit intraperitoneally with a solution of phenol-hydrazine and shortly after inoculation examined the blood from different parts of the body, including the ear. In every specimen many granular red corpuscles and many nucleated red cells were seen. From this experiment it was evident that the changes brought about by this drug affected the red cells of the whole circulation. He then repeated the same experiment, but before the drug was injected one ear was ligated. The blood was studied as before, being taken from various parts of the body as well as from the ligated ear. Specimens obtained from the body showed many granular red corpuscles and nucleated red cells, but in preparations made from the ligated ear granular cells were entirely absent, and nothing but normal blood elements were seen. In many of his experimental cases Schmidt found nucleated red cells the nucleus of which appeared to be undergoing various forms of dissolution; not only were they found in the peripheral circulation, but in the bone-marrow as well. He came to the conclusion that these basic-staining granules were the remnants of a broken nucleus, and that the process had its origin in the blood-forming organs and not in the general circulation.

[1] International Clinics, 1902, vol. i. p. 69.

[2] Exp. Beitr. z. Path. d. Blutes, Jenna, 1902.

Vaughan[1] studied the blood from normal individuals and from cases of both primary and secondary anæmias. He could demonstrate basic-staining granules in the erythrocytes of healthy persons and concluded that they were normally present in small numbers. Under certain pathological conditions they were increased, but no very great elevation was noted, excepting in blood containing many nucleated red corpuscles. He came to the conclusion that these granules were undoubtedly the product of a nucleus that had undergone dissolution.

In the routine examinations at the Pennsylvania Hospital of the blood of individuals poisoned by lead, nucleated red corpuscles were found so frequently in association with the granular cells, even when the total number of red corpuscles was only very slightly reduced, that it was thought there might be some relation between these two varieties of cells. The following study of the blood was undertaken with the object in view of determining if possible what this relation, if any, might be:

1. Blood of apparently normal individuals.
2. Eleven lead workers without subjective symptoms.
3. Sixteen cases of lead poisoning in the wards of the Pennsylvania Hospital.
4. Various forms of primary and secondary anæmias in the wards of the Pennsylvania Hospital.

The following examinations were made in each case:

1. Estimation of percentage of hæmoglobin.
2. Estimation of total number of erythrocytes per 1 cm.
3. Estimation of total number of leukocytes per 1 cm.
4. Differential count of 500 leukocytes and estimation of number of nucleated red corpuscles.
5. Estimation of percentage of red corpuscles containing basophilic granulations.

The hæmoglobin was estimated by Dare's hæmoglobinometer and the erythrocytes and leukocytes counted by means of the Thoma-Zeiss instrument. The differential leukocyte count was made after preparing smears on clean glass slides in the usual manner, and staining them with Wright's modification of Leishman's stain. In studying the basophilic granules Jenner's, Theonin-pheniqué, and Wright's stains were all tried, but none of them proved nearly as satisfactory as the method of using polychrome methylene blue recommended by Vaughan. This technique was therefore used in each case. The method as described by him is as follows:

"The ear of the patient whose blood we wish to examine is thoroughly cleansed of all dirt particles, by washing with alcohol. The blood is then drawn, the first drop being used as an index as to whether a free flow has been obtained or not. This is then wiped off with a clean towel and a drop of the previously filtered stain is placed over the site of puncture by means of a clean glass rod or pipette. The blood flowing from the wound then mixes directly with the stain without coming in contact with the air, and the small drop thus obtained is immediately collected on a cover-slip and placed at once upon a clean slide, where, if the drop is not too large and the slide and cover are clean, it spreads out into a thin film and may be examined at once." The stain used was Unna's polychrome methylene blue as prepared by Grübler.

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[1] Journal of Medical Research, vol. x. p. 342

In estimating the number of red cells containing granules with this method of staining a one-twelfth oil-immersion lens was used. One thousand red corpuscles were counted and the percentage of granular cells to non-granular cells calculated. It cannot be said that this is an absolutely accurate method, but after a little practice in staining the results will be quite uniform and only vary very slightly; in many instances not at all. This is by far the best method of studying the granules, as they can be very easily demonstrated when they exist in small numbers. It is the only method that I know of by which the granules can be found in normal blood. The blood of five apparently normal individuals was examined, and in each specimen red corpuscles containing basic-staining granules were present. Their number varied, in the different specimens examined, from 0.4 of 1 per cent. to 1.6 per cent. in 1000 red corpuscles counted. The hæmoglobin percentage and total number of red and white corpuscles were normal, while the red corpuscles containing granules, as well as those without granules, presented no abnormal changes. With Wright's stain granules could not be found in the red corpuscles.

TABLE I.—Lead Workers without Symptoms.

	Per ct. of hæmoglobin.	Red cells per 1 c.mm.	Per ct. of granular red cells.	Number of nucleated red cells found while counting 500 leukocytes	Remarks.
1	75	4,264,000	3.4	0	Exposure slight; never had symptoms.
2	70	3,400,000	2.8	3	" continuous and moderate for 18 years.
3	85	4,732,000	0.8	0	" very slight; never had symptoms.
4	80	3,256,000	9.6	1	" great; had one attack of colic.
5	70	4,116,000	5.6	1	" moderate; had one attack of colic.
6	70	4,300,000	5.3	1	" " " " " " "
7	90	4,040,000	3.7	0	" slight; never had symptoms.
8	70	3,404,000	4.0	1	" great; never had symptoms.
9	75	4,560,000	6.5	0	" great; marked tremor of hands.
10	90	3,800,000	3.6	1	" great; had one attack of colic.
11	90	4,808,000	1.3	0	" slight; never had symptoms.

Table I. shows the results of the examinations of the blood of eleven lead workers without subjective symptoms. All these examinations were made in the factory where the men were actually engaged at their various duties. The exposure varied somewhat in degree, but the men were all more or less exposed to lead dust while at work. On examining this table it will be seen at once that there was only a slight reduction of both the hæmoglobin and the total number of red corpuscles, and that they were reduced in the same relative proportions. Seven cases had a total red count of more than 4,000,000, the two highest of which is No. 3 and No. 11, while only four were below 4,000,000, the lowest being No. 4. All but two show a decided increase in the number of granular red corpuscles, while five cases presented one nucleated cell in the smear, and one presented three nucleated red cells. These cases certainly show a very mild type of anæmia, but still six of them had nucleated red corpuscles in their peripheral circulation.

TABLE II.—Sixteen Cases of Lead Poisoning in the Wards of the Pennsylvania Hospital.

	Per cent. of hæmoglobin.	Red cells per c.mm.	Leukocytes per c.mm.	Per cent. of red cells showing basophilic granules counting 1000 reds.	Number of normoblasts seen while counting 500 leukocytes.	Number of megaloblasts seen while counting 500 leukocytes.	Poikilocytosis.
1	72	2,828,000	7,500	18.0	4	0	Marked.
2	67	4,852,000	7,200	......	2	0	Moderate.
3	80	4,028,000	10,200	......	5	0	"
4	88	4,785,000	12,200	......	4	0	Slight.
5	76	4,400,000	8,500	......	2	0	"
6	98	4,680,000	7,300	......	2	0	Moderate.
7	70	2,620,000	6,200	5.0	2	0	Marked.
8	85	4,424,000	5,800	6.3	2	0	Slight.
9	78	4,472,000	12,550	13.0	3	0	"
10	82	4,672,000	9,450	9.5	1	0	"
11	76	3,800,000	7,000	14.0	130	13	Moderate.
12	76	3,860,000	7,500	9.2	75	9	"
13	76	3,850,000	7,400	18.0	10	0	"
14	82	4,056,000	5,800	......	2	0	Slight.
15	68	3,356,000	11,750	14.4	25	4	"
16	65	2.976,000	7,600	7.8	2	0	"

In Cases 2, 3, 4, 5, 6 and 14 granular cells were increased, but percentage not estimated.

Table II. gives the results of the blood examinations of sixteen cases of lead poisoning from the wards of the Pennsylvania Hospital.

All these cases presented the typical picture of poisoning: colic, constipation, blue line on gums, tremors of extremities, etc. One patient had wrist-drop. The symptoms were well defined in all cases, though in some they were more severe than in others. The hæmoglobin and number of red corpuscles were not reduced much more than in the previous series of cases. The red corpuscles in only three instances were below 3,000,000, although there were the most evident signs of poisoning.

TABLE III.—Ten Cases of Anæmia Including both Primary and Secondary Varieties.

	Per ct. of hæmoglobin.	Red cells per c.mm.	Leukocytes per c.mm.	Per ct. of red cells showing granulations in 1000 reds counted.	Number of normoblasts seen while counting 500 leukocytes.	Number of megaloblasts seen while counting 500 leukocytes.	Diagnosis.
1	22	980,000	5,600	0.2	2	0	Hodgkin's disease.
2	72	2,968,000	6,600	3.9	0	0	Carcinoma of stomach.
3	40	2,576,000	5,800	1.9	0	0	Fibroma of uterus.
4 Mar. 14	85	4,390,000	12,000	2.0	0	0	Phenacetin poisoning.
4 Mar. 16	80	3,728,000	11,000	2.8	0	0	Phenacetin poisoning.
4 Mar. 17	78	3,492,000	10,800	0.8	0	0	Phenacetin poisoning.
5	80	4,572,000	4,400	1.5	0	0	Carcinoma of liver.
6	50	2,380,000	9,000	2.8	0	0	Hypertrophic cirrhosis of liver.
7	60	2,984,000	....	3.9	0	0	Typhoid relapse.
8 May 5	30	1,824,000	6,900	10.3	2	0	" "
8 May 16	26	1,216,000	5,400	5.0	0	0	" "
8 May 24	27	1,328,000	5,900	5.2	0	0	" "
9	48	1,432,000	5,000	9.8	1 (250 leuk. counted)	0	Pernicious anæmia.
10	35	1,148,000	3,200	17.0	9 (250 leuk. counted)	6	Banti's disease.

The number of granular cells was decidedly increased in every case. There was, moreover, a much greater increase than in slides from lead workers presenting no subjective symptoms. This would naturally be expected. (In six of the cases the percentage of granular cells was not estimated, but it may be said that they were markedly increased in numbers.) Accompanying this increase of granular cells there was in each case one or more nucleated red corpuscles. In Nos. 11, 12, 13 and 15 enormous numbers of nucleated red corpuscles were found, some of them being typical megaloblasts.

In all of these cases of anæmia (Table III.) red corpuscles with granulations were invariably found and were increased slightly, while if the blood contained nucleated red corpuscles the increase was very marked.

The granules contained in the red corpuscles, in all the cases observed here, may be divided into three general classes, based upon their morphological appearance and their affinity for nuclear stains. These three groups I will call Nos. 1, 2 and 3.

1. Fine and coarse thread-like strands.
2. Fine dot-like granulations.
3. Dense coarse mass.

1. In the normal blood, when stained as previously described with polychrome methylene blue, a few red corpuscles were seen containing fine dot-like granules connected by delicate thread-like strands running irregularly through the cell. These strands varied in numbers and in length. Sometimes only one strand was seen in a cell extending through a quarter or the whole of its diameter, while other cells presented two or three such delicate threads often overlapping one another and suggesting in appearance a network. In color, they varied from a light lilac through all the intermediate shades to a dark blue. This type of granulation was seen in the blood of every case that was studied, whether normal or pathological, and was the predominating type present in the blood of primary and secondary anæmias, as well as of the more severe cases, due to lead poisoning. (See Plate, Fig. I., *a*.)

When the normal blood was stained by any other method these granulations could not be demonstrated.

2. The second variety of granulation was found in greatest numbers and most constantly in the blood of lead workers without symptoms, although constantly present in all the lead-poisoning cases studied and occasionally found in the primary anæmias.

These granulations varied from very minute, pinpoint-like granules to the size of an eosinophile granule, irregularly scattered throughout a red corpuscle, varying in color from a light blue to almost black. Sometimes there would only be four or five of these granules in a cell, but frequently they were so numerous that it was impossible to count them. The red corpuscles containing this type of granulation were of all varieties: microcytes, macrocytes, poikilocytes, polychromatophilic cells, and a few nucleated red corpuscles.

With Wright's stain they were easily and constantly found in all cases of lead poisoning and in a few of the primary anæmia cases. (See Plate, Figs. I., II., *b*, III.)

3. The third type was found in many instances of lead poisoning, but this particular form of granulation was perhaps more numerous than the other varieties in those cases of lead poisoning where

nucleated red corpuscles were plentiful. (See Cases Nos. 11, 12, 13 and 15, Table II.)

The red cells containing these granulations were, as a rule, normal in appearance, while others were smaller or larger than normal. There was never any change in shape.

The granules consisted of a dark-blue staining mass about the size of the nucleus of a normoblast. This mass was generally placed in the centre of the red cell, appeared distinctly granular, and was slightly ragged in outline. Occasionally one or two small blue granules, entirely separated from the central mass, were noticed near the periphery of the cell. (See Plate, Fig. I., *c*.)

I am convinced that these three varieties of granulations represent different stages in the dissolution of the nucleus of the red cell.

When Wright's stain was used many of the nucleated red corpuscles observed in smears taken from cases of lead poisoning presented small, blue-staining granules, scattered through their protoplasm. The color of these granules in every instance was the same as that of the nucleus. In a few instances the nucleus of the normoblasts stained poorly; its outline was somewhat indistinct, slightly ragged, and decidedly granular, suggesting that particles had been broken off from its edge. (See Plate, Fig. II., *d*.)

Many apparently normal red corpuscles containing a small, round, pale-blue, granular mass were noticed. Such cells might easily be interpreted as normoblasts, the nuclei of which had undergone some degenerative process. It was very difficult to distinguish these structures from platelets resting upon a normal red corpuscle, so that I am unprepared to diagnose this cell.

In one case of pernicious anæmia many megaloblasts were present, the nuclei of which were certainly breaking up, and many blue-staining granules were scattered throughout the protoplasm of the cell.

It is generally conceded by most observers that the presence of normoblasts and megaloblasts in the circulating blood is an indication of a regenerative process on the part of the blood-forming tissues, and by some the appearance of macrocytes and microcytes is interpreted in the same way.

In general, it may be said that nucleated red corpuscles are not present in the circulating blood unless there is a reduction of at least 50 per cent. of the total number of red corpuscles, and even then they occur only in small numbers.

Anæmia has always been spoken of as one of the characteristic signs of lead poisoning, but the exact degree of anæmia has very seldom been mentioned.

Red corpuscles containing basic granulations have frequently been found in the blood of experimental cases, and, as in Schmidt's experiments, nucleated red cells have occasionally been found. When the latter cells were present they were thought to indicate an acute and severe type of anæmia.

The blood counts of the cases presented here show that in lead poisoning there is, as a rule, only a mild type of secondary anæmia. In spite of this fact nucleated red cells may be present in the peripheral circulation. The characteristic pallor so common in patients suffering from this form of poisoning is probably referable not to the reduction of blood cells and hæmoglobin, but to some other cause, possibly a contraction of the peripheral bloodvessels.

Every case recorded in Table II. showed nucleated and granular red cells in the peripheral blood. The granular red cells were always increased in proportion to the number of nucleated cells present, and always seemed to hold a definite relation to them. Both varieties of red cells were more numerous in some cases, and decreased as convalescence was established. In many cases the intensity of the symptoms was not greater than in others, but still convalescence was much more protracted in those presenting great numbers of granular and nucleated red cells in the blood.

Vaughan, in his studies, was always able to demonstrate an increase in granular cells when there were present nucleated red corpuscles.

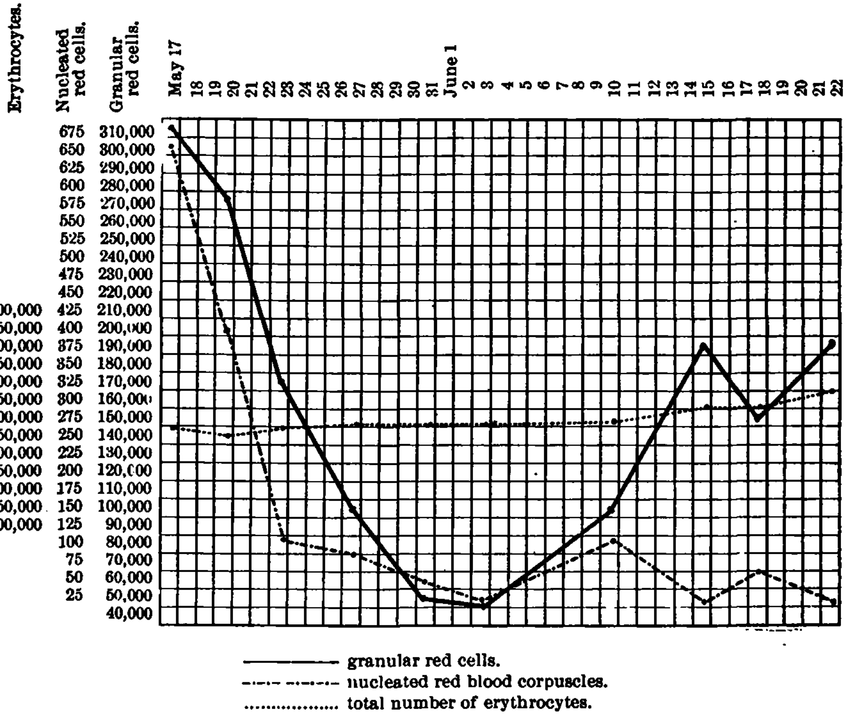
The constant association of the granules and nucleated red corpuscles lead me to believe that the granules are the remnants of a pre-existing nucleus, and that the three types of granulations described represent stages in the change from nucleated to non-nucleated red corpuscles. Of these probably No. 3 is the first, No. 2 the second, and No. 1 the last.

One of the arguments advanced to uphold the nuclear origin of the granules is the fact that they can only be demonstrated by means of nuclear stains. Simon, White, and Pepper have not been able to stain them with methyl green, which has always been classed as a specific nuclear stain, and thus they argue that this fact goes to prove that the granules are not of nuclear origin.

To determine this point many smears were made from cases of lead poisoning, and after brief fixation stained for five minutes with Ehrlich's methyl green and fuchsin mixture. The red cells took a very deep-red color and the granules a dark-brownish tint, so that the results were not satisfactory. A saturated watery solution of methyl green was then tried alone. Each smear was fixed for one minute at 120° C., stained one minute, and washed in water. On examining these specimens with a one-twelfth oil-immersion lens the protoplasm of the red cells appeared a yellowish color, showing no affinity for the green stain, while the nuclei of both leukocytes and normoblasts took a decided green color. The granules in the red corpuscles stained a beautiful green. (See Plate, Fig. III., *b*.) If the staining was prolonged more than one minute, the granules appeared almost black. This method of staining was carried out in all of the eleven cases shown in Table I., and in many others. In every case the granules were easily demonstrated. The stain used was methyl green as prepared by Grübler.

Demel, in 1901, and Donati, in 1903, stated that the erythrophile and cyanophile granules in red cells were identical, showing that if one variety was not found in a given specimen of blood, the other was also absent. Marzocchi[1] proved the identity of these granules by substituting the red stain for the blue, and *vice versa.* He stained a drop of blood diluted with salt solution with methylene blue, and then looked for the blue granules within the red cells. Then, keeping his eye on the same cell, he added a solution of neutral red in salt solution to the specimen under the cover-glass, when almost instantly the granules were seen to lose the blue and take up the red stain. The first colored fluid does not mix with the second, but flows from under the cover-glass in the opposite direction, so that the red dye is substituted for the blue.

CHART I.—*Lead Poisoning.*



In many cases I have been able to confirm these experiments and have succeeded in staining the granules satisfactorily by using a saturated solution of neutral red instead of the polychrome methylene blue, in the method described by Vaughan. Wright's stain was also tried in this way, and although the granules could be demonstrated the results were not so satisfactory as with the polychrome methylene blue.

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[1] Riforma Medica, January 23, 1904; quoted in New York and Philadelphia Medical Journal, February 20, 1904.

A series of blood counts was made in a case of lead poisoning from the wards of the hospital. This case was not more severe than the average. After being under treatment about three weeks the patient was discharged at his own request, presenting at that time no symptoms excepting marked tremors of hands. He immediately found employment (but not at his former occupation in lead works), and I was able to examine his blood during his dinner hour.

The granular cells and nucleated cells were counted as before described, and the total number of each per 1 c.mm. of blood calculated. The results of these observations are depicted in Chart I. The first count showed 650 nucleated red cells, 315,000 granular cells per 1 c.mm., while the total count of the erythrocytes was 3,496,000. It cannot be said that with such a high red count this enormous number of nucleated cells was entirely due to the anæmia.

For the first eighteen days the number of granular and nucleated red cells rapidly fell, and finally reached their lowest point while the patient was still under observation. After this there was an irregular rise and fall of both varieties of red corpuscles, the granular cells increasing rapidly just after the nucleated cells had reached their height. During all this time the total number of erythrocytes steadily increased.

Two more cases were studied in this way and results are shown in Charts II. and III. Chart II. shows the rise and fall of granular and nucleated red corpuscles in a fatal case of splenic anæmia and Chart III. is that of a severe case of pernicious anæmia.

These charts are of particular interest, inasmuch as they demonstrate that the rise in granular cells follows the elevation of the nucleated red blood corpuscles. When the elevation of nucleated red blood cells is at its height, the numbers of granular cells are low, but as the nucleated red cells fall the granular cells rise. That is, the increase of granular cells is synchronous with the decrease of nucleated red blood corpuscles.

The relation which these granular cells bear to the nucleated red blood corpuscles admits of at least two explanations. It is possible that the granules represent a degeneration of the protoplasm of the erythrocytes, as suggested by Grawitz, and that this extensive and diffuse degenerative process is accountable for the expulsion of nucleated red blood cells from the hæmopoietic organs. But under these circumstances one would hardly expect the elevation of nucleated red cells to precede the rise in granular cells. On the other hand, it is conceivable, as Schmidt claims, that the

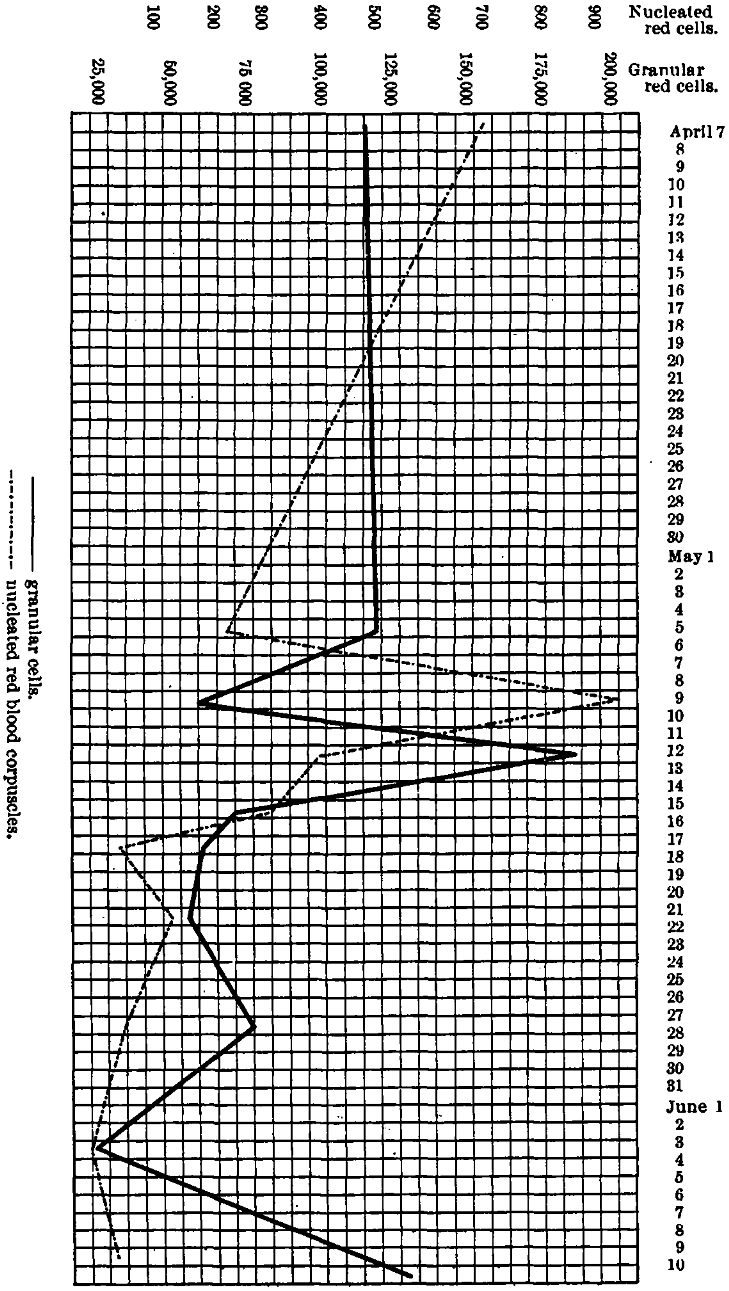
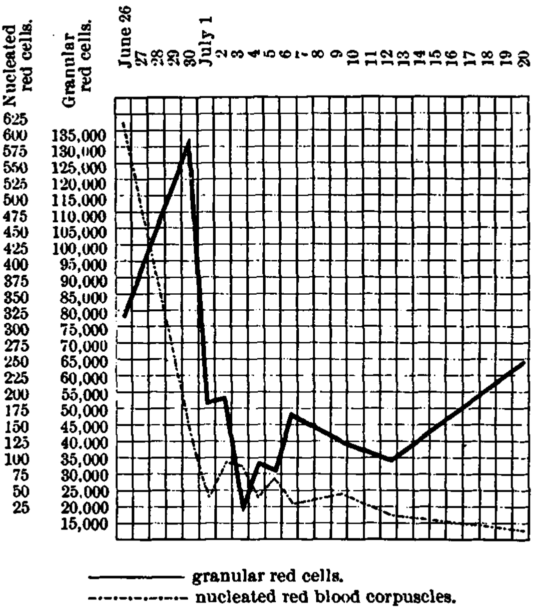


CHART II.—*Splenic Anæmia.*

granules are derived from the nucleus of the red cells, and that in lead poisoning the presence of nucleated red cells in the general circulation is due to some toxic effect of the drug upon the hæmopoietic organs. In this event one would expect, as the charts show, that the granular cells would increase in number as the nucleated red cells decreased. Indeed, the behavior of these two types of cells forms a strong argument in favor of the origin of the basophilic granules from the nuclei of the red blood corpuscles.

CHART III.—*Pernicious Anæmia.*



The total number of leukocytes in lead poisoning were, as a rule, normal; but many cases showed a slight decrease in the percentage of polymorphonuclear cells with an increase in the large mononuclear variety.

CONCLUSIONS.

1. Basophilic granules occurring in erythrocytes are normally present in small numbers in the blood of man, but may be increased in numbers under certain pathological conditions and decrease as convalescence is established.
2. Nucleated red corpuscles are common in the blood of those suffering from lead poisoning, and are always accompanied by an increase in the number of granular red cells.
3. The anæmia secondary to lead poisoning, as a rule, is only of a moderate degree.

4. The granular cells are most common in lead poisoning, possibly have their origin in the blood-forming tissues, and are probably the results of a fragmentation of the nucleus of the red blood corpuscle.

THE TOXÆMIA OF PREGNANCY.[1]

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Among the most important problems in obstetrics awaiting solution is the toxæmia of pregnancy.

The modern conception of this subject makes it responsible for eclampsia and probably for the pernicious nausea of pregnancy. We shall possibly understand better the grounds on which it is recognized if we consider briefly the modern conception of the physiology of pregnancy.

Pregnancy inevitably exposes the mother to danger. The fœtus by its syncytium invades not only the tissues of the maternal body, but frequently the blood current. In health the mother's immunizing substances in her blood serum keep the growth of fetal tissue within normal limits. If this boundary be passed clinical evidence leads us to recognize the transference of syncytial substances to the mother's blood as a potent cause of syncytioma malignum, pernicious nausea of pregnancy, and eclampsia.

Pregnancy induces marked abnormalities in the metabolism of the mother. Her enlarged thyroid illustrates the necessity for the increased production of the immunizing substances furnished by this gland. The anæmia and leukocytosis of early pregnancy draw attention to alterations in her blood. Changes in the heart muscle, in the parenchyma of the liver and kidneys show the effects of altered blood condition in these important structures. Altered pulse tension gives evidence of the abnormal condition of the nervous system. These conditions are so common in pregnancy that they are not usually considered as disease and frequently pass without detection. A pregnant woman is ordinarily said to be well if she passes through gestation without its premature interruption and without eclampsia. The balance between health and disease is rarely undisturbed.

The earliest manifestation of the toxæmia of pregnancy is seen in pernicious nausea. This has long been regarded as largely of reflex nature, caused by the irritation to the nervous system of the

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[1] Read before the Luzerne County Medical Society, November 16, 1904.